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Developmental Exposure to Perfluorohexane Sulfonate (PFHxS) Induces Hypothyroxinemia in Rat Dams and Offspring: Examination of Thyroid Gland and Behavior

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Thyroid hormones (TH) are critical for normal mammalian brain development. In humans, low maternal serum thyroxine (T4) levels are associated with neurological deficiencies and cognitive impairment. Perfluorinated chemicals are widely distributed xenobiotics with varying effects on TH. In this study, perfluorohexane sulfonate (PFHxS, 0, 0.05, 5 or 25 mg/kg/day) was administered (p.o.) to Wistar rat dams (n = 20/dose group) from gestation day (GD) 7 through postnatal day (PND) 22. Maternal serum T4 was reduced to 80 and 60 % of control by GD 15 in the 5 and 25 mg/kg/day dose groups. Further reductions to 60 and 30 % of control were evident by PND 22. Serum T4 in offspring assessed on PND16/17 was reduced to 70 and 55 % of control in these same dose groups. No signs of overt toxicity were observed in the dams or the pups. Liver weights were not affected in the dams or male pups on PND 16, with mild increases (3-6%) detected in the female pups on PND 17 at 5 and 25 mg/kg/day. Despite reductions in serum TH, thyroid gland weights were not increased in dams or pups. Neither were the transcriptional levels of *Tpo*, *Nis*, *Nkx2* or *TshR* altered in the thyroid gland of pups suggesting a lack of activation of the hypothalamic-pituitary-thyroid axis. Motor activity assessed on PND 27 and PND 115 (n=15-19/dose/sex/age) was only nominally affected. No increases in thyroid gland weight and unaltered gene transcription suggest that the thyroid gland is not a direct target for PFHxS-induced hypothyroxinemia. Modest changes in liver weight also fail to implicate upregulation of hepatic metabolism as a target of PFHxS. Further investigations of the mechanisms whereby PFHxS reduces serum TH, its toxicological profile, and its potential to induce developmental neurotoxicity are warranted. *Does not reflect EPA policy.*